EXHIBIT F

DEPOSITION EXHIBIT 40

1. TITLE PAGE

Study Title: Clinical assessment of feasibility, complications and effectiveness at twelve months, three years and five years of the TVM technique for genital prolapse.

Scope of Report:	Presentation of data up to and including 12 months post-procedure.
Report Version: Date	Final: 27 June 2006
Study Code	CT-TVM-001-03
Study Indication	Genital prolapse, Stage III or greater requiring both anterior and posterior repair
Investigational Procedure	Trans-Vaginal Mesh (TVM) technique using GYNECARE *GYNEMESH* PS* (Nonabsorbable *PROLENE** Soft Mesh)
Location of Study	Eight investigational sites in France
Phase of Study	Post-marketing
Principal Investigator	PR. Michel Cosson, Hôpital Jeanne de Flandre - Chirurgie Gynécologique, Lille, France
Sponsor:	Ethicon Global Medical Affairs with addresses at: Ethicon SAS, 1 rue Camille Desmoulins TSA 81002, 92787 Issy les Moulineaux Cedex 9 Johnson & Johnson Medical Ltd., PO Box 1988, Simpson Parkway, Kirkton Campus, Livingston EH54 0AB, UK Ethicon Inc., PO Box 151, Route 22 West, Somerville, NJ 08876-0151, US
Sponsor Contact:	David Robinson, MD
First patient screened:	23 January 2004
Last patient completed: (12-month follow-up)	06 January 2006

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2. STUDY SYNOPSIS

Name of Sponsor Company Ethicon Global Medical Affairs	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Trans-Vaginal Mesh (TVM) technique using GYNECARE GYNEMESH* PS	Volume Page	

Study Number: CT-TVM-001-03	
Study Title: Clinical assessment of feasibility, complications and effectiveness at twelve months, three years and five years of the TVM technique for genital prolapse.	
Principal Investigator: PR. Michel Cosson, Hôpital Jeanne de Flandre - ChirurgieGynécologique, Lille, France.	
Study Centre(s): Eight investigational sites in France.	
Publication Reference: Not applicable.	
Study Period: First patient screened: 23 January 2004 Last patient completed: 06 January 2006 (12-month follow-up)	**Phase of Development:** Post-marketing.
Objectives: The objective of the study was to demonstrate the usability of GYNECARE GYNEMESH* PS PROLENE* Nonabsorbable Soft Mesh for anterior, posterior and vault prolapse repair using the Trans-Vaginal Mesh (TVM) technique.	
Study Design: This was a non-randomised, non-controlled observational study involving routine pre-operative assessment, surgery and follow-up care.	
Number of Patients (planned and analysed): It was planned to recruit 90 female patients in order to obtain an evaluable group of 82 patients. Each investigator was to recruit at least 10 and, at most, 40 patients. Ninety (90) patients were enrolled into the study. All 90 patients underwent surgical correction of their prolapse with TVM and had post-operative effectiveness data and were therefore included in the full analysis set.	

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Diagnosis and Main Criteria for Inclusion: The following selection criteria were defined in the study protocol:

1. Patient was a candidate for anterior and posterior surgical repair of the pelvic floor. Required to have a symptomatic prolapse of at least International Continence Society (ICS) Stage III as defined in Appendix A of the study protocol (Appendix 16.1.1).
2. Patient was at least 21 years of age.
3. Patient did not wish to have more children.
4. Previous or simultaneous hysterectomy. Uterus not retained.
5. Absence of uncontrolled diabetes.
6. No coagulation abnormality.

Study Product, Mode of Administration, Batch Number: Sufficient units of GYNECARE GYNEMESH* PS were supplied to the investigators for use in the study. These units were pre-cut according to a standard template.

Detailed guidelines for the treatment of pelvic organ prolapse using the TVM prosthetic repair technique were provided in the study protocol.

The product supplied for the study was Lot No. JCG 03265, expiry date 2008-09.

Duration of Treatment: The investigational device was administered during surgery for prolapse repair.

Comparator Product: None.

Criteria for Evaluation: The primary objective was evaluated by determination of the proportion of patients in which correction of the prolapse was achieved (ICS Stage 0 or I). Failure of correction was defined as ICS Stage II or higher, or a surgical re-intervention to repair a recurrence of vaginal prolapse.

Secondary evaluation criteria were the assessment of:

- Vaginal prolapse occurring in an area not treated with the GYNEMESH.
- Peri-operative complications.
- Patient tolerance of the synthetic mesh inserted.
- Post-operative complications.
- Quality of life (QOL).

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Statistical Methods: The full analysis set was defined to be as close to the ideal of including all subjects (intention-to-treat principle). Subjects were to be excluded from the full analysis set for the following reasons:

i) They had not received TVM (*i.e.* they were not in the safety analysis set).

ii) No post-operative effectiveness data were available.

This was not a comparative study, therefore only two-sided 90% and 95% confidence intervals (CI) were estimated. The criterion for success was that the upper 90% two-tailed CI (same as the tail on a one tail 95% CI) did not exceed 20%. Otherwise, the study would be deemed a failure, as it would not show that the prolapse rate was <20%.

Calculation of recurrence was based on the stage from the Vaginal Prolapse Scoring System (POP-Q) score. Stages 0 and I were considered no recurrence (providing additional surgery did not indicate a recurrence), while stages II, III and IV were considered recurrence.

The patient questionnaire included a prolapse-specific component (PSI), which was calculated from questions 1-11. The maximum score was 44 with lower scores indicating better improvements. Questions 12-15 described the impact of the symptoms on daily activities of living and provided the QOL score. A maximum of 16 was possible with lower scores better.

No a priori statistical analysis of safety variables was planned. Safety data were summarised and adverse events were coded to aid summarising the data.

Results and Conclusions: The primary effectiveness variable was recurrence of prolapse at 12 months post-procedure (failure of procedure), with failure being defined as a prolapse of ICS Stage II or more or a surgical re-intervention. The results show a failure rate at 12 months of 18.4% with a 90% CI of 11.9-26.6. Thus the study did not meet the pre-defined criteria of a failure rate of less than 20% (upper limit of 90% CI). Of the 16 failures there was only one patient with a prolapse of ICS Stage III; fifteen patients had prolapse of ICS Stage II. In 10 of the Stage II patients, the leading edge of the prolapse was inside the introitus.

The secondary effectiveness parameters show a failure rate at 6 months of 12.6% (90% CI: 7.3, 20.1). Other secondary effectiveness parameters show a reduction in the number of patients reporting sexual activity limited by prolapse at 12 months compared with baseline (29 [32.2%] *vs* 6 [6.9%]). The incidence of dyspareunia in those patients who were sexually active was 4/61 (7%) at baseline, 8/42 (20%) at 6 months and 3/40 (8%) at 12 months (Tables 14.2.8.2 and 14.2.4.1). One patient (3004) was reported as having dyspareunia at baseline but was not sexually active due to prolapse. The 3 cases of dyspareunia at 12 months were all new onset. Dyspareunia was resolved at 12 months in the 5 patients who reported the condition at baseline.

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Results and Conclusions (continued):

Moderate or severe vaginal retraction was reported in 11 (12.6%) patients. Visible or visible and palpable mesh exposure was reported in 9 patients during the 12-month follow-up, 5 of whom underwent surgical intervention. One other patient had additional examinations (uretroscystoscopies, rectoscopies) but had not received surgery for the mesh exposure.

Substantial improvements in QOL were observed. Improvements in prolapse symptoms were indicated by a reduction in PSI scores from 13.9, standard deviation (SD) 5.7 at baseline to 1.9, SD 2.5 at 12 months. Activities of daily living QOL scores also improved over the 12-month study period (3.4, SD 3.1 to 0.4, SD 1.0).

The intra-operative complication rate in this study was low (5.6%). The major post-operative complication reported at 6 weeks was urinary infection (15 [16.9%] patients). Haematoma and abscess were reported by 4 (4.5%) and one (1.1%) patient respectively. One case of vesico vaginal fistula, which resolved with surgery, was reported. Twenty-seven SAEs were reported and 18 of these were considered probably related to the study device or procedure.

In conclusion, while this study did not meet the stringent predefined statistical criteria in terms of demonstrating an incidence of prolapse recurrence at 12 months of below 20%, the absolute rate of 18.4% (with a 90% CI of 11.9-26.6) demonstrates the invaluable role of TVM in treating patients with vaginal prolapse in terms of reasonable success rates and a lower rate of recurrence/re-operation compared to other published studies. Significant improvements in QOL, particularly with respect to the PSI, were observed and activities of daily living QOL scores also improved over the 12-month study period. Furthermore, mesh exposure rates (10.0%) and complication rates were low. The safety data also demonstrate a predictable safety profile with a favourable benefit/risk ratio for patients requiring treatment for vaginal prolapse.

Further follow-up of these patients to 5 years post-procedure is planned.

Date of Report: 27 June 2006

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3. CONTENTS

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

>	More Than
<	Less Than
AFSSAPS	French Health Products Safety Agency
BMI	Body Mass Index
CCPPRB	Consultation Committee for the Protection of Persons in Biomedical Research
CI	Confidence Interval
cm	Centimetre
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Record Form
CRO	Contract Research Organisation
dy	Day
g	Gram
HRT	Hormone Replacement Therapy
ICS	International Continence Society
IEC	Independent Ethics Committee
kg	Kilogram
LOCF	Last observation carried forward
m	Metre
mo	Month
POP-Q	Pelvic Organ Prolapse-Quantification
PSI	Prolapse Symptom Inventory
QA	Quality Assurance
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUI	Stress Urinary Incontinence
Tab	Tablet
TVM	Trans-Vaginal Mesh Prosthetic Repair Technique
TVT	Tension-Free Vaginal Tape
TVT-O	TVT-obturator
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
wk	Week

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5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC)

The study protocol (18 June 2003) and informed consent documentation was submitted to the Lille Consultation Committee for the Protection of Persons in Biomedical Research (CCPPRB) and a favourable opinion was issued following on 01 July 2003. Two revised versions of the protocol (12 May 2004, 04 May 2006) were submitted to the IEC for information. Details of protocol changes are given in Section 9.8.1.

5.2 ETHICAL CONDUCT OF THE STUDY

A declaration of intent for the conduct of the study was submitted to the French Health Products Safety Agency (AFSSAPS) on 16 July 2003 and registered under the No. 2003/07/008.

The devices used for the study had already been granted marketing authorisation for the location of all participating centres. The protocol complied with the requirements appearing in the legal stipulations about the device.

The sponsor held a public/product liability insurance policy for the duration of the study from ACE Insurance No. 1 052 441.

All study and patient information was to remain strictly confidential. Patients had a right of access to their data provided by French law (Computing and Freedom) at any time through the investigator.

Financials contracts between the sponsor and investigators were submitted to the French Medical Association (Conseil National de l'Ordre des Médecins) for review on 05 November 2003. An amended financial contract was sent on 22 July 2004.

5.3 PATIENT INFORMATION AND CONSENT

Prior to taking part in the study patients were fully informed about the project and their consent to participation was an indispensable condition for their recruitment. A patient information sheet, which had been approved by the IEC, provided details of what participation in the study would involve and the expected risks and benefits. Patients were informed that, should they take part in the study, they were free withdraw at any time without explanation and without affecting the quality of care they would receive. Patients were required to personally sign a consent form to confirm that they had been given sufficient time and opportunity to discuss the study and ask questions and that they consented to allow access to their medical records by authorised study personnel.

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6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a multicentre study in which eight investigational sites in France participated (Text Table 1). The Principal Co-ordinating Investigator was PR. Michel Cosson.

TEXT TABLE 1: INVESTIGATORS AND INVESTIGATIONAL SITES

Site	Principal Investigator	Co-investigator(s)	Site Address
01	Dr Juan Berrocal		Clinique de l'Europe, 61 bd de l'Europe, 76100 ROUEN
02	Dr Philippe Debodinance		Sce de Gynécologie-Obstétrique, C.H Dunkerque, Maternité Les Bazennes, 41, rue des Pinsons 59430 SAINT POL SUR MER
03	Dr Henri Clave		Clinique St Antoine, 7 avenue Durante 06100 NICE
04	Professeur Michel Cosson	Dr J-Ph Lucot Dr Pierre Collinet	Hôpital Jeanne de Flandre - Chirurgie Gynécologique, CHRU de Lille, 2, avenue Oscar Lambret - 59037 LILLE Cedex
05	Professeur Bernard Jacquetin	Dr Joël Amblard Dr Brigitte Fatton	Maternité Hôtel Dieu, CHU de Clermont-Ferrand, Boulevard Léon Malfreyt 63058 CLERMONT FERRAND Cedex 1
06	Dr Olivier Garbin	Dr Michel Hummel	SIHCUS- Centre Médico Chirurgical et Obstétrical, Service de Gynécologie 19, rue Louis Pasteur, BP 120 67303 SCHILTIGHEIM Cedex
07	Dr Claude Rosenthal		Clinique Saint-Germain, 12 Bd Painlevé 19316 BRIVE Cedex
08	Dr Richard Villet	Dr Delphine Salet-Lizee	Hôpital des Diaconesses Croix Saint Simon, Site de Reuilly, Chirurgie Viscérale&Gynécologique, 18 Rue du Sergent Bauchat 75571 PARIS CEDEX 12

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Project management, data management and quality assurance (QA) were undertaken by Ethicon personnel. A number of Contract Research Organisations (CRO) and independent consultants were involved in study activities. Details are provided in Appendix 16.1.4, Table A1.

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7. INTRODUCTION

Pelvic floor prolapse is a general term used to describe various clinical conditions that are associated with pelvic floor relaxation in female patients. The clinical manifestations include:

- Anterior vaginal prolapse (medial and/or lateral cystocele).
- Posterior vaginal wall prolapse (rectocele).
- Vault prolapse (enterocele, uterine prolapse, and vaginal vault prolapse).

Pelvic floor prolapse is thought to result from a stretching, weakening or tearing of the soft tissue structures that support the pelvic organs. These tissues become compromised because of a weakened or damaged *levator ani* muscle group. This muscle group is the platform at the base of the pelvis responsible for supporting the pelvic organs. It works with the connective tissues to support these organs. As the *levator ani* is damaged and drops, the opening between the *levator ani* is widened. Intra-abdominal forces are then relatively unopposed by the weakened muscle. These increased forces are applied to the connective tissue support structures, which results in their tearing or stretching. Risk factors for pelvic floor prolapse include vaginal parity, neuropathy, obesity, chronic or excessive recourse to the valsava manoeuvre, connective tissue disorders, prior surgery, oestrogen status and advancing age [1-4]. Of the factors identified, vaginal parity and its associated neuropathy appear to play the biggest role in pelvic floor disorders [2]. Damage to the nerves supplying the *levator ani* during childbirth result in weakening of muscle and subsequent prolapse of the organs. Surgical correction of these problems is a major health-care issue for women. An analysis of members of a large health maintenance organisation estimated a lifetime risk of 11.1% of at least one operation for pelvic organ prolapse and urinary incontinence with a re-operation rate of 29.2% [5]. These numbers have been confirmed in other studies [6-9].

Non-surgical interventions for prolapse management include pelvic floor exercises and pessary support. Surgical options are many and are made more challenging as multiple weakened regions often occur in a patient and incomplete correction of any may lead to worsening of the others. The surgical procedures may involve tightening and reinforcing of weakened tissue, suspension of unsupported structures or a combination of both. The tightening/reinforcing and suspension procedure may utilise several materials including:

- Suture alone.

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- Autologous tissue
- Cadaverous material
- Allograft material
- Xenograft material
- Synthetic absorbable mesh
- Synthetic permanent mesh.

Synthetic meshes, which were first used for abdominal wall hernias, are often produced from materials originally used for sutures. They are able to provide support where autologous tissues are not adequate, but they do add the risks of erosion and rejection [10]. Synthetic materials have been used with increasing frequency in gynaecological surgery over the past 30 years [11]. Reinforcement of tissue is sought because of the weakened state of the patient's own tissue. These grafts may be placed using an abdominal or vaginal approach. Only one prospective, randomised study has been performed which compared the vaginal to abdominal approach for treating pelvic organ prolapse. This study found twice the failure rate using a vaginal approach [6].

Literature reviews describing the outcome and complications associated with pelvic floor repair procedures are inconclusive. In cases where meshes were used to provide additional support, advantages have been reported. Julian studied patients with multiple recurrence of vaginal prolapse in two groups that differed by mesh use or not. In his study, all grafts were placed using a vaginal approach. He found a decrease in the expected recurrence rate with mesh, but did observe some complications associated with the use of synthetic mesh. The erosion rate was 25%. Overall, he concluded that adding synthetic mesh was effective in these cases [12]. Visco reported an overall vaginal mesh erosion rate of 5.5% using an abdominal approach for mesh placement. This rate was considered low when compared to historical data, which shows a 9% erosion rate for abdominal mesh placement [13].

Polypropylene mesh has been the most widely used mesh in gynaecological surgery including many types of pelvic floor repair procedures [14]. Polypropylene meshes include BARD MARLEX Mesh and Ethicon PROLENE Polypropylene Mesh. A surgical protocol for the treatment of pelvic organ prolapse using GYNECARE GYNEMESH* PS has been developed (TVM [Trans-Vaginal Mesh] Prosthetic Repair Technique) and the current study was designed to demonstrate the feasibility of this technique for treatment of the anterior wall, posterior wall and vaginal vault. A similar study was running concurrently in the US (Protocol Number 2003-016).

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This report presents the study results up to and including follow-up at 12 months post-procedure.

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8. STUDY OBJECTIVES

The objective of the study was to demonstrate the usability of GYNECARE GYNEMESH* PS PROLENE* Nonabsorbable Soft Mesh for anterior, posterior and vault prolapse repair.

This objective was evaluated by determination of the proportion of patients in which correction of the prolapse was achieved (International Continence Society [ICS] Stage 0 or I). The proportion of patients failing to achieve a correction of prolapse was to be reported. Failure of correction was defined as ICS Stage II or higher, or a surgical re-intervention to repair a recurrence of vaginal prolapse. The ICS staging criteria are provided in Appendix A of the study protocol (Appendix 16.1.1).

Secondary evaluation criteria were the assessment of:

- Peri-operative complications.
- Patient tolerance of the synthetic mesh inserted.
- Post-operative complications.
- Quality of life (QOL).

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9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

This was a non-randomised, non-controlled observational study into which it was planned to enrol approximately 90 patients. It was planned to recruit 90 female patients in order to obtain an evaluable group of 82 patients. Each investigator was to recruit at least 10 and at most 40 patients. The study involved routine pre-operative assessment, surgery and follow-up care. The observation schedule was as follows:

- Pre-operative Assessment (Visit 1)
- Informed consent process.
- Patient demographics including age, height and weight. Body Mass Index (BMI) was automatically calculated as weight/(height)^2 at data entry.
- Confirmation of selection criteria.
- Number of vaginal deliveries, number of Caesarean deliveries.
- Smoking history ('Never smoked', 'Smoked regularly > 5 years ago', Smoked regularly < 5 years ago, 'Currently smokes < one packet per day', 'Currently smokes one packet or more per day').
- Concomitant diseases ('Diabetes', 'Hypertension', Heart disease', 'Chronic obstructive pulmonary disease (COPD)', 'Connective tissue disease', 'History of severe, chronic constipation', 'Other').
- Previous gynaecological and general surgery ('hysterectomy', 'surgery for incontinence', 'surgery for prolapse', 'inguinal hernia repair', incisional hernia repair', 'other').
- Number of years since menopause.
- Hormone treatment ('None', 'Topical oestrogen', 'Systemic hormone replacement therapy [HRT]', ' Topical and systemic treatment').
- Impact of prolapse on sexual activity (Section 9.5.1).
- Assessment of incontinence (Stamey Incontinence Grade) (Section 9.5.1).
- Clinical examination of the vaginal mucosa including bladder neck mobility (Section 9.5.1).
- Information on pain reported by patient (Section 9.5.1).
- Prolapse Assessment using the Vaginal Prolapse Scoring System (POP-Q) (Section 9.5.1).

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- Prolapse Symptom Inventory (PSI), Quality of Life (QOL) Assessment & Visual Analogue Scale (VAS) (Section 9.5.1).

Operative Assessment

The following details of the operative procedure were recorded:

- Date and duration of procedure
- Operation performed ('Anterior and posterior treatment', Other')
- Route ('Vaginal', Vaginal & transgluteal', Other)
- Fixation of mesh onto vaginal wall ('None', 'Posterior only', 'Anterior only', 'Both posterior & anterior')
- Treatment/prophylaxis of urinary incontinence ('None', 'TVT', 'TVT-obturator [TVT-O]', 'Other technique')
- Resection of excess vaginal tissue ('None'/'Minimum')

Additional operations performed and comments on the manipulation of the mesh were recorded if appropriate. Peri-operative adverse events were ascertained (Section 9.5).

Convalescence Assessment (6 weeks ± 2 weeks) (Visit 2)

The following parameters were ascertained for the 6-week convalescence period:

- Assessment of complications (Section 9.5).
- Number of days before resumption of activity.
- Number of days not at work (if appropriate).
- Number of days catheterised - determined from the first post-operative day on which the patient could empty her bladder (<100 cc residual) without using a catheter.
- Resumption of sexual activity ('Yes','No').
- Sexual relations satisfactory ('Yes', 'No').

6-month Follow-up Clinical & QOL Assessments (±1 month) (Visit 3)

- POP-Q Prolapse Assessment.
- Assessment of mesh exposure and action taken (Section 9.5.1).

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- Assessment of incontinence (Stamey Incontinence Grade).
- Information on pain reported by patient.
- Impact of prolapse on sexual activity.
- Clinical examination of the vaginal mucosa and bladder neck mobility.
- Assessment of vaginal retraction and description of any visible anatomical distortion.
- Assessment of complications (Section 9.5).
- PSI, QOL and VAS.

The clinical and QOL assessments carried out at six months were repeated at the 12-month (±1 month) assessment (Visit 4).

At the time of this report, follow-up in the study was continuing and the clinical and QOL assessments were scheduled to be repeated at the following timepoints:

- 3 years (±2 month)
- 5 years (±2 month)

Details of any additional gynaecological procedures, including description of the procedure, setting, anaesthesia requirements, reason for the procedure and result of procedure) were recorded at post-operative visits.

All data collected for each case was recorded in the appropriate Case Report Form (CRF).

The efficacy and safety parameters assessed are described in more detail in Section 9.5.

This report presents the data up to and including the 12-month post-procedure assessment, which includes the primary efficacy assessment. The end of study will be when the last participant has completed the follow-up evaluation at five years post-procedure.

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FIGURE 1: STUDY SCHEDULE

Study Day	Pre-operative	Operative Assessment	Follow-up				
Visit	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Timepoint			6 Week	6 Month	1 Year	3 Year	5 Year
Informed Consent	X						
Demographics	X						
Selection Criteria	X						
Pregnancy & Smoking History	X						
Concomitant Diseases	X						
Menopause Status & hormone Treatment	X						
Previous Gynaecological & General Surgery	X						
Observations on Sexual Activity & Continence	X			X	X	X	X
Clinical Examination & Bladder Neck Mobility	X			X	X	X	X
Pain Assessment	X			X	X	X	X
POP-Q Scores	X			X	X	X	X
Surgical Details		X					
Peri-operative Adverse Events		X					
Adverse Events & Additional Surgery			X	X	X	X	X
PSI, QOL & VAS				X	X	X	X
Convalescence Assessment			X				
Later Procedures Assessment				X	X	X	X

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9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This was an observational study without randomisation or a control group in which patients underwent a routine pre-operative assessment, surgery and follow-up care. All patients who agreed to participate were included in the study in such a way as to obtain a consecutive series.

The criterion for success was that the prolapse failure rate, defined as a prolapse of ICS Stage II or higher as evidenced by POP-Q scores, or a surgical re-intervention to repair a recurrence of vaginal prolapse, did not exceed 20% of the study population. The design of the study was considered appropriate to achieve the aim of generating further data on the usability of GYNECARE GYNEMESH* PS PROLENE* Nonabsorbable Soft Mesh for anterior, posterior and vault prolapse repair.

9.3 SELECTION OF STUDY POPULATION

9.3.1 INCLUSION CRITERIA

The following selection criteria were defined in the study protocol:

1. Patient was a candidate for anterior and posterior surgical repair of the pelvic floor. Required to have a prolapse symptomatic of at least ICS Stage III as defined in Appendix A of the study protocol (Appendix 16.1.1).
2. Patient was at least 21 years of age.
3. Patient did not wish to have more children.
4. Previous or simultaneous hysterectomy. Uterus not retained.
5. Absence of uncontrolled diabetes.
6. No coagulation abnormality.

Patients who met the selection criteria and who had given their consent to participation in the study by signing a declaration of informed consent were included. Information relating to all the patients contacted for inclusion in the study was recorded on a selection form and the reason for non-participation for every patient who did not take part in the study was to be specified.

9.3.2 EXCLUSION CRITERIA

No specific exclusion criteria were defined in the study protocol.

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9.3.3 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were instructed during the informed consent process that participation in the study was voluntary and that even if they agreed to participate they were free to withdraw at any time without explanation. This would not affect the quality of care they received then or in the future.

Patients could be withdrawn from the study for the following reasons:

- Patient lost to follow-up.
- Patient withdrew consent.

Patients would not be withdrawn from the study based on prolapse surgery failure (POP-Q scores ≥ II). These patients were to continue to be seen throughout the study for the required visits.

Although not formally documented until the protocol revision dated 04 May 2006 (Section 9.8.1), these criteria for withdrawal were adhered to throughout the study.

The investigators responsible for the study had the right to stop the study for medical or other reasons.

9.4 ADMINISTRATION OF MEDICAL DEVICE AND CONCOMITANT TREATMENTS

9.4.1 PROCEDURES

Detailed guidelines for the treatment of pelvic organ prolapse using the TVM prosthetic repair technique were provided in Appendix B of the study protocol (Appendix 16.1.1).

A hysterectomy was systematically performed according to surgeon preference if the patient had not already undergone one.

Treatment or prevention of urinary incontinence was optional and could be performed by a urethral incision distinct from the anterior vaginal incision. The prosthesis would be a polypropylene band positioned at the mid-urethra. The route and method of insertion were not specified.

Vaginal packing was optional up to the next but one day following the procedure. A urinary catheter of the Folley type Charriere 16 was left in place until removal of the mesh.

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9.4.2 IDENTITY OF INVESTIGATIONAL DEVICE

GYNECARE GYNEMESH* PS is constructed of knitted filaments of extruded polypropylene. The mesh affords excellent strength, durability and surgical adaptability with sufficient porosity for necessary tissue ingrowth. The mesh is knitted by a process which interlinks each fibre junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unravelling. The bi-directional elastic property allows adaption to various stresses encountered in the body.

9.4.3 SUPPLY AND ACCOUNTABILITY OF INVESTIGATIONAL DEVICE

Sufficient units of GYNECARE GYNEMESH* PS were supplied to the investigators for use in the study. These units were pre-cut according to a standard template and were to be used only for patients included in the study. The investigators were required to keep up-to-date accountability records of units supplied and unused devices were to be returned to the Sponsor.

The product supplied for the study was Lot No. JCG 03265, expiry date 2008-09.

The label for the clinical investigation supplies included the study number and the statement 'Exclusively for Clinical Investigations' in addition to the full CE Mark product details.

9.4.4 ANAESTHESIA AND ANTIBIOTIC PROPHYLAXIS

General or loco-regional anaesthesia could be used. Systematic peri-operative antibiotic prophylaxis in accordance with the surgeon's preference was permitted and was to be recorded in the surgical report. Post-operative antibiotic therapy had to be justified. If infiltration of the vaginal wall by a vasoconstrictive solution was used, dosages and maximum quantity were to be defined in the surgical report.

9.4.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

All patients received GYNECARE GYNEMESH* PS (Nonabsorbable PROLENE* Soft Mesh)

9.4.6 PRIOR AND CONCOMITANT THERAPY

The use of topical oestrogen and systemic HRT was recorded in the CRF as part of the pre-operative assessment.

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The administration of peri-operative antibiotic prophylaxis and infiltration of the vaginal wall by a vasoconstrictive solution was to be recorded in the surgeon's report.

No other medications were recorded.

9.4.7 PROCEDURE COMPLIANCE

The procedure was carried out by a qualified and experienced surgeon.

9.5 EFFECTIVENESS AND SAFETY VARIABLES

9.5.1 EFFECTIVENESS AND SAFETY MEASUREMENTS ASSESSED AND STUDY SCHEDULE

9.5.1.1 EFFECTIVENESS MEASUREMENTS

Recurrence of Prolapse

This was assessed using the POP-Q scoring system. This is a standard system to describe pelvic organ prolapse in women and dysfunction of the pelvic floor [15]. The patient is examined and the positions of a number of pre-defined reference points are measured as centimeters above or proximal to the hymen (negative number) or as centimetres below or distal to the hymen (positive number), with the plane of the hymen being defined as zero (0). All measurements are recorded as whole numbers. From this quantitative description the prolapse can be staged between Stage 0 and Stage IV. Details of prolapse classification are provided in Appendix A of the study protocol (Appendix 16.1.1).

In this study recurrence was specified as a prolapse of Stage II, III or IV and this was considered a failure of the procedure.

Any surgical re-intervention to repair a recurrence of vaginal prolapse (as indicated from a review of additional operations prior to database lock) was also considered a failure.

Prolapse Stage

This was assessed at all timepoints using the POP-Q scoring system as described above.

Impact on Sexual Activity

This was assessed at all timepoints on a 4-point scale as follows:

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- 1=No impact.
- 2=Sexually active, bothered by prolapse.
- 3=Not sexually active, because of prolapse.
- 4=Not sexually active, for another reason.

Impact on incontinence (Stamey Incontinence Score)

This was graded at all timepoints on a 4-point scale as follows:

- 1=continent (dry).
- 2=Passes urine with effort.
- 3=Passes urine with minimum effort.
- 4=Passes urine constantly

Vaginal mucosa

This was assessed at all timepoints by clinical examination as:

- Healthy.

or

- Significantly atrophic.

Vaginal retraction/compliance

This was assessed at all timepoints by clinical examination as:

- No retraction (0).
- Slight retraction (+).
- Moderate retraction (++).
- Severe retraction (+++).

Bladder neck mobility

This was assessed by clinical examination as:

- Normal.
- Hypermobile.
- Fixed.

Hypermobility was defined as movement >30 degrees with effort or A in Q-tip test.

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Pain

If the patient complained of vaginal pain the presence or absence of each of the following types of pain was recorded:

- Unprovoked.
- Provoked during the examination.
- Provoked, dyspareunia.
- Provoked, cystalgia.
- Provoked during defaecation
- Provoked, other.

Mesh exposure and operation

Exposure of mesh was ascertained at post-procedure study visits and was classified as:

- No exposure.
- Inflammatory tissue without exposure.
- Palpable.
- Visible.
- Both palpable and visible.

Size and localisation of any exposure were recorded. Treatment was recorded as:

- No treatment.
- Conservative treatment.
- Surgical treatment – an additional surgery form was completed.

Quality of life

Described in Section 9.5.1.2.

9.5.1.2 QUALITY OF LIFE MEASUREMENTS

A validated prolapse-specific quality of life (QOL) instrument was used as a post-operative subjective outcome measure. The questionnaires were administered by the investigators who recorded the patients' responses in the CRF[1].

[1] One co-investigator at Site 05 asked the patients to complete the questionnaires themselves.

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The questionnaire comprised 16 questions and responses were scored as follows:

0 = Never.
1 = Rarely
2 = Sometimes
3 = Most of the time.
4 = All of the time.

Questions 1 to 11 related to symptoms associated with the prolapse and provide the Prolapse Symptom Inventory (PSI) score. Questions 12 to 15 described the impact of the symptoms on daily activities of living and provided the QOL score. Details of the scoring system and calculation performed are given in Section 9.7.1.1.

In addition patients were asked two questions to which they responded by marking a 10 cm horizontal visual analogue scale (VAS). The questions were:

- Specify to what extent your prolapse has affected your life. The extreme left of the line was annotated (in French) 'Not at all' and the extreme right 'Affects everything I do all the time'.
- Specify how pleased you are with the operation. The extreme left of the line was annotated (in French) 'Very dissatisfied' and the extreme right 'Satisfied in every respect'.

Patients were asked to respond to the questions by marking the appropriate VAS with a short vertical line at a point on the line which they felt most appropriately described their situation.

9.5.1.3 *SAFETY MEASUREMENTS*

Safety was assessed by the occurrence of adverse events and complications. An adverse event was defined as any untoward medical occurrence not present at baseline.

Information recorded in the CRF included onset and resolved dates, intensity ('Mild', 'Moderate', 'Severe'), treatment required ('Yes', 'No' and details of treatment if appropriate), outcome ('Recovered', 'Recovered with sequelae' 'Ongoing', 'Death') and relationship to the device or the procedure ('Probable', 'Possible', 'Not related', 'Not evaluated'). The investigator made the assessment of causality.

Adverse events were assessed as serious or not. A serious adverse event

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(SAE) was defined as any untoward occurrence that:

- Resulted in death.
- Was life-threatening.
- Required inpatient hospitalisation or prolongation of existing hospitalisation.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly or birth defect.

Any event not included in the above that required medical or surgical intervention to prevent one of the above outcomes was also considered to be a SAE.

Deaths, life-threatening events and other SAEs that may have been related to the mesh or the procedure were to be notified to the Pharmaceutical & Regulatory Affairs Associated Director at Ethicon SAS as soon as possible, but at the latest within a period of five days after the event had been observed. Adverse events related to the mesh were also to be reported to Ethicon SAS. Ethicon SAS was responsible for reporting SAEs that may have been related to the mesh or the procedure to the Regulatory Authority (AFSSAPS).

Peri-operative adverse events were classified as follows:

- None.
- Bladder perforation.
- Rectal perforation.
- Severed ureter.
- Haemorrhage (>500 ml).
- Other.

Post-operative adverse events collected at the 6-week convalescence visit were classified as:

- Urinary infection.
- Haematoma.
- Abscess.
- Other.

Details of additional gynaecological procedures carried out during the follow-up period were recorded.

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9.5.2 APPROPRIATENESS OF MEASUREMENTS

The POP-Q assessment and stage classification of prolapse used in the study are endorsed by the ICS, the American Urogynecologic Society and the Society of Gynecologic Surgeons for the description of female pelvic organ prolapse and pelvic floor dysfunction. It contains an objective site-specific system for describing, quantifying and staging pelvic support in women and has been developed for use in individual patients and populations of patients [15].

The QOL assessment was based on a validated prolapse-specific instrument [16].

9.5.3 PRIMARY EFFECTIVENESS VARIABLE

The primary effectiveness variable considered in this report is the recurrence rate of prolapse at 12 months post-procedure. This information was recorded by the POP-Q score, with the stage of organ prolapse of II to IV or a surgical re-intervention to repair a recurrence of vaginal prolapse (as indicated from a review of additional operations prior to database lock) being considered a failure.

9.6 DATA QUALITY ASSURANCE

Training

During initiation of each of the sites, a training session involving the investigator was conducted. This involved review of the study protocol, CRF completion and the study related procedures. No specific training for the POP-Q assessment of prolapse was undertaken at initiation. However training videos were supplied to study sites in February 2004 and a DVD of this information (Duke University Medical Centre DVD, Organ Prolapse Quantification Examination) was sent to each site on 06 October 2005.

During the course of the study, the sites were visited regularly by the study monitor to ensure compliance with the protocol. During these visits all data recorded in the CRF were checked against source documents.

Monitoring

The study monitor visited the sites at regular intervals to review the CRFs and other study findings. These reviews aimed to verify compliance with the protocol and that the findings reported were complete.

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Data Management

Data were entered into the Oracle Clinical (Version 4.5.0) database by Ethicon personnel. Data were double-entered by two independent operators and inconsistencies between the two entries were resolved. Electronic edit checks were then run against the data and queries issued to site for clarification. Edit checks were predefined in a Data Management Plan. At the end of the study 100% quality control checks were made on primary effectiveness and adverse event parameters to ensure a 0% error rate in these fields.

Audits

Two audit visits were performed at Site 04 (27 May 2005) and at Site 01 (19 October 2005). The purpose of these audits was to ensure compliance with the protocol and relevant standards. During the audit the Investigator Study File and a selection of CRFs were reviewed.

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9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 STATISTICAL ANALYSIS PLAN

The statistical methods to be used were documented in a Statistical Analysis Plan (SAP), which was finalised on 03 February 2006 before the database was locked on 28 February 2006 (Appendix 16.1.9.). Following review of adverse event coding, the database corrected and final lock was on 29 May 2006. The statistical analyses were carried out according to the SAP and as described in the following sections.

9.7.1.1 EFFECTIVENESS AND BASELINE EVALUATION

Analysis Sets

The following effectiveness analysis sets were defined:

i) Enrolled analysis set

ii) Full analysis set.

iii) Per-protocol set

The enrolled analysis set was defined as all patients enrolled into the study.

The full analysis set was defined to be as close to the ideal of including all subjects (intention-to-treat principle). Subjects were excluded from the full analysis set for the following reasons:

i) They had not received TVM (*i.e.* they were not in the safety set).

ii) No post-operative effectiveness data were available.

The per-protocol analysis set comprised all subjects in the full analysis set without major protocol deviations. Major deviations were agreed at the pre-database lock meeting.

The concurrent hysterectomy set (Hyst analysis set) comprised all patients in the full analysis set that underwent a concurrent hysterectomy.

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Effectiveness Variables

The following primary and secondary variables were investigated in the evaluation of effectiveness:

The primary effectiveness variable was recurrence rate of prolapse at 12 months. This information was recorded by the POP-Q score, with the stage of organ prolapse of II to IV or a surgical re-intervention to repair a recurrence of vaginal prolapse (as indicated from a review of additional operations prior to database lock) being considered a failure.

The following were secondary variables:

- Prolapse recurrence at 6 months, 3 years and 5 years.
- Prolapse stage (all timepoints).
- Impact on sexual activity (all timepoints).
- Impact on incontinence (all timepoints).
- Vaginal mucosa (all timepoints).
- Vaginal retraction/compliance (all timepoints).
- Bladder neck mobility (all timepoints).
- Pain (all timepoints).
- Mesh exposure and operation (all timepoints).
- Quality of life (see below, all timepoints, including QOL score and PSI)
- Stamey incontinence score (assessment of incontinence, just a summary of the question) (all timepoints).

Quality of life calculations

The following calculations were made [16],

The PSI was calculated from questions 1-11. Each question had a score of 0 (Never), 1 (Rarely), 2 (Sometimes), 3 (Most of the time) or 4 (All the time). These individual scores were added to give a total of between 0-44, with lower scores indicating a better outcome.

The QOL score associated with these symptoms was calculated from questions 12-15 which had the same scoring system, hence a total score of between 0-16 was possible. Again lower scores indicated a better outcome.

Since there was no guidance for handling missing data, any missing data resulted in a missing total score. Individual items were also tabulated.

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Additional Analyses

The SAP indicated that exploratory data summaries may be produced to identify whether a learning effect was present.

Methods of Analysis

All analyses/summaries were produced using SAS® (Version 9.1.3 Cary, NC, USA).

Estimation and significance testing

This was not a comparative study, therefore only two-sided 90% and 95% confidence intervals (CI) were estimated. The study would be deemed a success providing the upper 90% two-tailed CI (same as the tail on a one tail 95% CI) did not exceed 20%. Otherwise, the study would be a failure, as it would not show that the prolapse rate was <20%.

Calculation of recurrence was based on the stage from the POP-Q score. Stages 0 and I were considered no recurrence (providing additional surgery did not indicate a recurrence), while stages II, III and IV were considered recurrence.

Demographic and other baseline characteristics

Demographic and other baseline characteristics were summarised descriptively for the full analysis set of subjects. The following characteristics were summarised:

i) Age
ii) Height
iii) Weight
iv) Body Mass Index
v) Smoking
vi) Births (any, caesarean)
vii) Concomitant diseases

Surgery details

The following were summarised descriptively for the safety set of subjects:

i) Surgery History
ii) Operation duration
iii) Nights in hospital

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iv) Post-op nights in hospital
v) Prolapse operation
vi) Mesh fixation (if data available)
vii) Treatment of urinary incontinence
viii) Resection of vaginal tissue

Primary effectiveness analysis

A 90% and 95% two-tailed CI of the recurrence rate was constructed.

Secondary effectiveness analysis

Data were summarised using mean, median, standard deviation (SD), minimum and maximum or frequencies as appropriate.

9.7.1.2 SAFETY EVALUATION

Analysis Set

All subjects receiving TVM were included in the safety analysis set.

Safety Variables

The following were listed and summarised

i) Adverse events (summary by coded terms)
ii) Intra-operative complications
iii) Post-operative complications

Methods of Analysis

No statistical analysis of safety variables was carried out. Data were summarised and adverse events were coded to aid summarising the data.

9.7.1.3 DATA PRESENTATION

Tables, Figures and Listings

Data were tabulated where appropriate by visit. Continuous data summaries present (unless stated otherwise) number of observations, number of missing observations (if there are any), mean, standard deviation, minimum, median and maximum. Categorical data summaries present the number of

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observations and the corresponding percentage. Listings are presented in centre, subject, visit, date and time order using the data from all randomised subjects:

9.7.2 SAMPLE SIZE

It was planned to will recruit 90 patients with a projected evaluable group of 82 patients. Each investigator was to enrol a minimum of 10 and a maximum of 40 patients into the study.

Calculation of sample size took the following factors into account. The aim of the study was to show that the proportion of failures (recurrence of prolapse) among women who had undergone surgery to treat pelvic organ prolapse did not exceed 20%. The hypotheses to be tested were:

H_0: $P \geq +0.20$

H_1: $P < 0.20$

where P=proportion of failures in the population studied.

This calculation assumes:

α significance level = 0.05 (one way)

Power = $1-\beta$ = 80%

P_0 = 0.20 and P_1 = 0.10 (the minimum difference [Δ] to be detected was 0.10)

With these assumptions and using a binomial test for H_0 versus H_1, it was calculated that 82 evaluable subjects would be necessary.

The CI for the recurrence rate incidence was calculated to be as follows:

N = 82

Number of evaluable subjects = 82			
No of incidents	**Recurrence Rate**	**95% CI**	**Determination**
4	0.05	0 to 0.11	Success
8	0.10	0 to 0.172	Success
9	0.11	0 to 0.184	Success
10	0.12	0 to 0.198	Success
11	0.13	0 to 0.212	Failure

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9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1 CHANGES IN THE CONDUCT OF THE STUDY

9.8.1.1 PROTOCOL AMENDMENTS

A Revised Protocol (12 May 2004) was issued in which minor changes were made to the wording of the description of the surgical technique. The changes related to:

- Limited sagittal colpotomy.
- Bowel preparation.
- Optional Vaseline and betadine-coated intra-rectal mesh.

The sample size calculation was clarified and the number of evaluable patients required from 90 recruited into the study was calculated to be 82.

It was documented that adverse effects of TVM were to be notified to the GYNECARE Director of Technical and Regulatory Affairs in France.

Further clarifications to the protocol were documented in an administrative change to the protocol (04 May 2006). These included:

- Clarification that failure was defined as Stage II or higher prolapse, as evidenced by total POP-Q scores, or a surgical re-intervention to repair a recurrence of vaginal prolapse.
- Extension of recruitment period from four to ten months.
- Further details of the planned statistical analysis and clarification that the full analysis would be performed after all subjects had completed the 12-month follow up and additional analyses would be performed at three and five years post-procedure.
- Correction of the scoring of the incontinence assessment scale from 0, 1, 3, 4 to 1, 2, 3, 4.
- Revision of information to be collected on additional gynaecological procedures to be consistent with concurrent US study.
- Insertion of a section to clarify that patients would be withdrawn from the study for the following reasons:
  - Patient lost to follow-up
  - Patient withdrew consent.

  Patients would not be withdrawn from the study based on prolapse surgery failure (POP-Q scores equal or greater than 2). These patients would continue to be seen throughout the study for the required visits.

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Additional patient visits not required by the protocol but related to the patient's prolapse surgery were to be recorded in the source documentation and on the subsequent procedures form.

9.8.2 STATISTICAL ANALYSES

9.8.2.1 CHANGES FROM PROTOCOL TO SAP

Details of the primary endpoint were clarified. The only secondary effectiveness endpoint specified in the protocol was QOL; all other secondary effectiveness endpoints were defined and described in the SAP.

9.8.2.2 CHANGES FROM SAP

No PP analysis was carried out as none of the protocol deviations identified before database lock was deemed to be major.

Unplanned analyses (signed rank test) were performed for the changes from baseline of the PSI and QOL scores.

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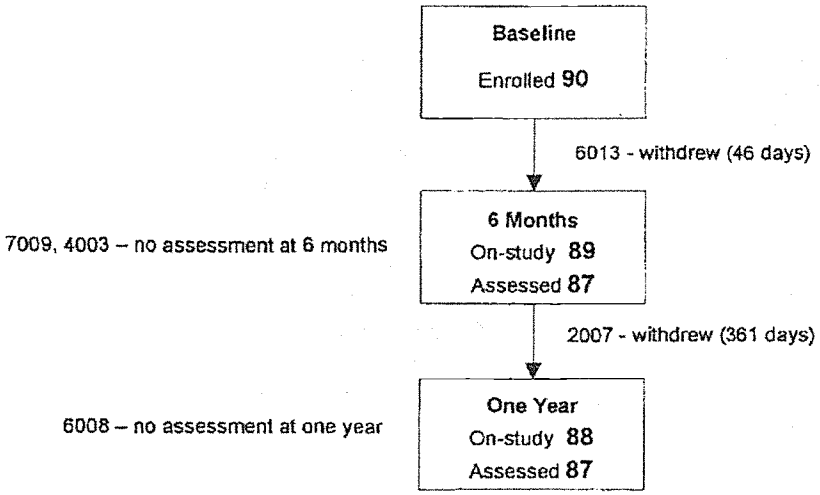
10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

Ninety (90) patients were recruited from 8 centres in France. Each centre recruited between 5 and 17 patients (Table 14.1.1.1, Appendix 16.2.1.1). Two patients withdrew from the study; patient 2007 did not want to attend for further study visits and was lost to follow-up, patient 6013 did not wish to continue in the study and was followed-up outside of the study protocol (Appendix 16.2.1.1, Figure 2). These patients withdrew at 361 and 46 days respectively from the date of the study procedure. Patient 6008 did not attend the 12-month assessment but it is anticipated she will be reviewed at the 3-year visit.

The disposition of patients is shown in Figure 2.

FIGURE 2: DISPOSITION OF PATIENTS



Source: Appendices16.2.1.1 and 16.2.1.2

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Bladder neck mobility

Bladder neck mobility is summarised by visit in Table 14.2.7.1 and data are listed in Appendix 16.2.6.2. Hypermobility was recorded for 45 (50.0%) patients pre-operatively and this decreased to 14 (16.1%) patients at 6 months and 9 (10.3%) patients at 12 months.

Pain

The incidence of vaginal pain by visit, including any pain, pain during examination and dyspareunia is summarised in Tables 14.2.8.1, 14.2.8.2 and 14.2.8.3 and data are listed in Appendix 16.2.6.3. The incidence of dyspareunia in those patients who were sexually active was 4/61 (7%) at baseline, 8/42 (20%) at 6 months and 3/40 (8%) at 12 months (Tables 14.2.8.2 and 14.2.4.1, Figure 14.4). In addition, one patient (3004) who was reported as having dyspareunia at baseline was not sexually active due to prolapse and the pain associated with sexual activity. The 3 cases of dyspareunia at 12 months were all new onset. Dyspareunia was resolved at 12 months in the 5 patients who reported the condition at baseline.

Dyspareunia change from baseline is summarised in Table 14.2.8.3. This shows that for the 5 patients that had baseline dyspareunia, this was resolved at 6 months for 4 patients and at 12 months none reported the condition. New onset dyspareunia was reported in 7 patients at 6 months and in 3 patients at 12 months.

Mesh exposure and operation

Mesh exposure, determined by vaginal examination at 6 and 12 months, is summarised for the full analysis set in Table 14.2.9.1 and for the concurrent hysterectomy set in Table 14.2.9.2. Data are listed in Appendix 16.2.6.4. At 6 months there were 9 (10.3%) cases of palpable mesh exposure, 2 (2.3%) cases of visible mesh exposure and 2 (2.3%) cases of exposure that was both visible and palpable. At 12 months there were 8 (9.2%) cases of palpable mesh exposure. Five patients underwent surgical intervention; one patient (5003) had additional examinations (uretroscystoscopies, rectoscopies) but did not receive surgery for the mesh exposure.

In the concurrent hysterectomy set there were 8 (11.3%) cases of palpable mesh exposure and 2 (2.8%) cases of visible and palpable mesh exposure at 6 months. At 12 months there were 7 (10.1%) cases of palpable mesh exposure. Four patients underwent surgical intervention; patient 5003 had additional examinations (uretrocystoscopies, rectoscopies).

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For the purpose of ascertaining complications, mesh exposure defined as visible or visible and palpable at any point during the 12-month period was included and reported as an adverse event (Appendix 16.2.7.3). Palpable alone was not deemed to be mesh exposure, as the mesh remained covered by vaginal tissue. On this basis of this definition, 9 patients (10.0%) experienced mesh exposure that was reported as a complication during the 12-month follow-up period.

11.4.1.3 QUALITY OF LIFE (INCLUDING PSI AND QOL SCORES)

Prolapse Symptom Inventory (PSI)

The PSI comprised questions 1 – 11 of the patient questionnaire. Lower scores are better and the maximum possible score is 44. Total PSI scores are summarised in Table 14.2.3.1 and by POP-Q stage in Table 14.1.3.2. Data are summarised by question and visit in Tables 14.2.3.3 to 14.2.3.8. PSI data are listed in Appendices 16.2.6.7 and 16.2.6.8.

The mean PSI score was 13.9 (SD 5.7) pre-operatively and this was reduced to 3.1 (SD 3.4) at 6 months and 1.9 (SD 2.5) at 12 months, indicating a reduction in symptomatic effects of prolapse over the post-operative period.

Statistical analysis of the change from baseline of the PSI, using the signed rank test, indicated that this change was statistically significant ($p<0.001$) (Appendix 16.1.9.2.1).

Quality of Life (QOL)

The QOL assessment comprised questions 12 – 15 of the patient questionnaire. Lower scores are better and the maximum possible score is 16. Total QOL scores are summarised in Table 14.2.3.9 and by POP-Q stage in Table 14.2.3.10. Data are summarised by question and visit in Tables 14.2.3.11 and 14.2.3.12. QOL data are listed in Appendix 16.2.6.8.

The mean QOL score was fairly low pre-operatively (3.4, SD 3.1) indicating that, for most patients, daily living activities were not affected to any great extent by their prolapse. However the scores decreased further post-operatively to an average of 0.8 (SD 1.6) at six months and 0.4 (SD 1.0) at 12 months.

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Statistical analysis of the change from baseline of the QOL, using the signed rank test, indicated that this change was statistically significant ($p<0.001$) (Appendix 16.1.9.2.2).

Visual Analogue Scales (VAS)

Data are summarised in Tables 14.2.2.1 and 14.2.2.2 and listed in Appendix 16.2.6.7.

Patients appeared to find completion of the two VAS confusing due to the way they were presented in the CRF and the inconsistency in the scoring (one VAS scored 'best to worst' left to right and the other scored 'worst to best' left to right). The results obtained should therefore be viewed with caution.

11.4.2 STATISTICAL/ANALYTICAL ISSUES

11.4.2.1 ADJUSTMENT FOR COVARIATES

Not applicable.

11.4.2.2 HANDLING OF DROPOUTS OR MISSING DATA

Missing data for prolapse recurrence was estimated using two methods.

- Last post-treatment observation carried forward (LOCF) (patients with no post-treatment POP-Q data did not have missing data estimated)
- Assuming missing was a recurrence.

Analyses taking missing data into account by these methods are summarised in Table 14.2.1.1

For the QOL calculations any missing data for a patient resulted in a missing total score.

11.4.2.3 INTERIM ANALYSIS AND DATA MONITORING

Two unplanned interim analyses have been carried out previously. An interim analysis based on 6-month data for the first 40 patients from the current French study, together with 29 patients recruited into a similar study in the US was completed on 04 February 2005. This included the POP-Q stage primary endpoint. A further interim analysis of data from 171 patients from the US and French studies combined was carried out in July 2005. The current report is confined to the presentation of data from the French study; a separate report

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is planned for the presentation of the US data. Therefore it was not considered appropriate to present the French and US combined data from these interim analyses here.

Follow-up analyses will be carried out at 3 and 5 years and reported in addenda to this report. For each analysis, only data up to the relevant time point will be included.

11.4.2.4 MULTICENTRE STUDIES

For the primary endpoint, success rates within centres ranged from 100% (Centres 01 and 02), to 64% (Centre 04) and 50% (Centre 06). Details are given in Table 14.2.1.4.

11.4.2.5 MULTIPLE COMPARISON / MULTIPLICITY

Not applicable

11.4.3 TABULATION OF INDIVIDUAL RESPONSE DATA

POP-Q scores and assessment of success/failure are listed by patient in Appendix 16.2.6.5.

11.4.4 EFFICACY CONCLUSIONS

The primary effectiveness variable was recurrence of prolapse at 12 months post-procedure (failure of procedure), with failure being defined as a prolapse of ICS Stage II or more or a surgical re-intervention. The results show a failure rate at 12 months of 18.4% with a 90% CI of 11.9-26.6. Thus the study did not meet the predefined criteria of a failure rate of less than 20% (upper limit of 90% CI). However, of the 16 patients categorised as failures there was only one patient with a prolapse of ICS Stage III; 15 patients had prolapse of ICS Stage II. In 10 of the anatomical failures the leading edge was inside the introitus. Difference between centres were seen with success rates ranging from 100% (Centres 01 and 02), to 64% (Centre 04) and 50% (Centre 06).

The secondary effectiveness parameters show a failure rate at 6 months of 12.6% (90% CI: 7.3, 20.1). Other secondary effectiveness parameters show a reduction in the number of patients reporting sexual activity limited by prolapse at 12 months compared with baseline (29 [32.2%] *vs* 6 [6.9%]). The incidence of dyspareunia in those patients who were sexually active was 4/61 (7%) at baseline, 8/42 (20%) at 6 months and 3/40 (8%) at 12 months. One patient (3004) was reported as having dyspareunia at baseline but was not sexually

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active due to prolapse. The 3 cases of dyspareunia at 12 months were all new onset. Dyspareunia was resolved at 12 months in the 5 patients who reported the condition at baseline.

Moderate or severe vaginal retraction was reported in 11 (12.6%) patients at 12 months. Nine patients (10.0%) experienced visible or visible and palpable mesh exposure during the 12-month follow-up period and 5 patients underwent surgical intervention.

Substantial improvements in QOL were observed. Improvements in prolapse symptoms were indicated by a reduction in PSI scores from 13.9 (SD 5.7) at baseline to 1.9 (SD 2.5) at 12 months. Activities of daily living QOL scores also improved over the 12-month study period (3.4 [SD 3.1] to 0.4 [SD 1.0]).

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12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

All patients enrolled into the study underwent the TVM prolapse repair procedure and all are included in the safety analysis set. One patient (5003) had anterior TVM only.

12.2 ADVERSE EVENTS

12.2.1 BRIEF SUMMARY OF ADVERSE EVENTS

A total of 131 adverse events were reported during the study. The numbers of patients experiencing adverse events are summarised in Text Table 6 and Table 14.3.1.4. Two patients withdrew from the study at 46 and 361 days.

TEXT TABLE 6: NUMBER OF PATIENTS EXPERIENCING ON-TREATMENT ADVERSE EVENTS, SAES, SEVERE ADVERSE EVENTS, RELATED ADVERSE EVENTS OR ADVERSE EVENTS REQUIRING TREATMENT

Number of adverse events	131
Number of SAEs	27
Number of patients (%) experiencing at least one:	
Adverse event	68 (75.6)
SAE	23 (25.6)
Severe adverse event	9 (10.0)
Adverse event requiring treatment	45 (50.0)
Related adverse event	60 (66.7)

Safety analysis set: n=90

Source: Table 14.3.1.4

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Adverse events occurring during the 12-month follow-up period in more than 5% of patients are summarised in Text Table 7.

TEXT TABLE 7: ADVERSE EVENTS (CODED TERM) OCCURRING IN MORE THAN 5% OF PATIENTS

Coded Term	N=90 Number (%)
UTI	20 (22.2)
Urinary Incontinence	24 (26.7)
Anterior Prolapse	16 (17.8)
Pain	14 (15.6)
Mesh exposure	[1]10 (11.1)
Dyspareunia	6 (6.7)

1 Patient 5007 had an adverse event coded as mesh exposure. The verbatim term was 'inflammatory area with prosthetic fragment palpable not visible at the vagina'. This did not meet the criteria of visible or visible & palpable for inclusion in the secondary endpoint of mesh exposure (Section 11.4.1.2)

Source: Table 14.3.1.5

Five (5.6%) patients experienced intra-operative adverse events (Table 14.3.1.2, Appendix 16.2.7.2); one patient experienced rectal perforation, 2 patients experienced haemorrhage and 2 patients experienced intra-operative adverse events classified as 'Other' (one urinary retention and one vaginal perforation)

At the 6-week assessment urinary infection was reported as a post-operative complication by 15 (16.9%) patients (Table 14.3.1.3, Appendix 16.2.6.1). Haematoma and abscess were reported by 4 (4.5%) and one (1.1%) patient respectively. Twenty-five (28.1%) patients reported a post-operative complication classified as 'Other', including one occurrence of vesico vaginal fistula. Details are provided in Appendix 16.2.6.9.

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12.2.2 DISPLAY OF ADVERSE EVENTS

Adverse event summaries are presented in Tables 14.3.1.2 (intra-operative adverse events), 14.3.1.3 (post-operative complications), 14.3.1.4 (number of patients experiencing adverse events) and 14.3.1.5 (summary of on-treatment adverse events by coded term).

12.2.3 ANALYSIS OF ADVERSE EVENTS

No analysis was planned or undertaken.

12.2.4 LISTING OF ADVERSE EVENTS BY PATIENT

Adverse events are listed by patient in Appendix 16.2.7.3.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 LISTING OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1.1 DEATHS

No deaths occurred during the study.

12.3.1.2 OTHER SERIOUS ADVERSE EVENTS

Twenty-three (25.6%) patients reported 27 SAEs. These are described in detail in Section 12.3.3, Text Table 8.

12.3.2 OTHER SIGNIFICANT ADVERSE EVENTS

No adverse events resulted in withdrawal from the study.

12.3.3 NARRATIVES OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

SAEs are noted in the adverse event listing in Appendix 16.2.7.3 and additional information is listed in Appendix 16.2.7.4. Details of all SAEs including onset and resolved dates, outcome, relationship to either the device or the procedure, serious category and comments on treatment are presented in Text Table 8.

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TEXT TABLE 8: SERIOUS ADVERSE EVENTS

Patient	Event as Reported	Onset-Resolved Dates	Outcome	Relationship	(Serious Category) Comments
1003	Vesico vaginal fistula	25Jun04-03Sep04	Recovered	Excluded	(Hospitalisation & Surgical/medical intervention) Bladder catheter & intervention on 11Aug04. Fistula closed by vaginal way. Procedure failed. Complications exceptional – vaginal wall shrinkage.
1003	Ureteral stenosis	11Aug04-25Aug04	Recovered	Excluded	(Surgical/medical intervention) 25Aug04 Further vesico vaginal fistula repair-uretro-vesical reimplantation.
1005	De novo incontinence	07Aug04-21Oct04	Recovered	Probable	(Surgical/medical intervention) Repair with TVT transobturator on 21Oct2004.
1006	Urinary retention	02Jun04-20Sep04	Recovered	Probable	(Surgical/medical intervention) 01Jul04-prothesis section TVTO. Colpoperineorrhaphy & release of the mesh.
1009	De novo incontinence	27Jun04-05Oct04	Recovered	Probable	(Surgical/medical intervention) Repair with TVT transobturator on 05Oct04
2001	Post-operative perineal haematoma	09Feb04-12Feb04	Recovered	Excluded	(Hospitalisation) Augmentin 2 g/dy for 8 wk; Flagyl 2 tab/dy for 8 dy; Spedafolsine + Tandyferon 2 g/dy for 1 mo.

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Patient	Event as Reported	Onset-Resolved Dates	Outcome	Relationship	(Serious Category) Comments
3004	Imperfect scar at 5 weeks after surgery. Mesh erosion (3 months).	24Sep04-11Oct04	Recovered with sequelae	Probable	(Surgical/medical intervention) Exeresis (general anaesthesia) of the part of the mesh (2x1 cm) eroded with colpectomy & anterior colporrhaphy. Discrete cystocele anterior at 6 mo.
3006	Mesh erosion at the back of the vagina & stress urinary incontinence	03Sep04-27Sep04	Recovered with sequelae	Probable	(Surgical/medical intervention) Resection of the mesh extruded. Colporrhaphy & transobturator suburethral tape.
3006	SUI	20Jul04-27Sep04	Recovered with sequelae	Probable	(Surgical/medical intervention) Resection of the mesh extruded (4x4 cm at top of vagina). Colporrhaphy & transobturator suburethral tape.
3008	Fracture of the neck of femur	25Jan05-16Nov05	Recovered	Excluded	(Hospitalisation) Surgical treatment.
3009	Urinary incontinence	10Jan05-29Sep05	Recovered	Probable	(Surgical/medical intervention) Suburethral sling put in place by transobturator approach.
4001	Genital prolapse recurrence	24Jun04-24May05	Recovered	Probable	(Surgical/medical intervention) Surgical procedure – promontory fixation celioscopy. Small asymptomatic cystocele persists.
4001	Suspicion of no vaginal cicatrisation	28Feb05-28Feb05	Recovered	Excluded	(Hospitalisation) Examination with local anaesthesia-normal, no treatment.

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Patient	Event as Reported	Onset-Resolved Dates	Outcome	Relationship	(Serious Category) Comments
4003	Fracture of the neck of the femur	10Nov04-08Feb05	Recovered	Excluded	(Hospitalisation, surgical/medical intervention)
5001	Hepatic colic	02Feb05-18Feb05	Recovered	Excluded	(Hospitalisation) Cholescystectomy with complete anaesthesia by colioscopy.
5002	Adhesion of the vaginal fourchette	25Mar05-24May05	Recovered	Excluded	(Hospitalisation) Re-intervention (perineal plasty). Section of a small adhesion of the left vaginal fundus and an adhesion of the vulvo-vaginal fourchette.
5003	Recurring urinary infection – dysuria & macroscopic haematuria	10Dec04-	Ongoing	Probable	(Surgical/medical intervention) 04Mar05:Urethrocystoscopy with vesical biopsy (discrete inflammatory chronic lesion without tumour. Trigone deformed by the mesh underlying). 05Jul05: New surgical exploration urethrocystoscopy rectoscopy vulva biopsy. Urinary leaks explained by a local collection probably between prosthesis and bladder eliminated by a small sub-trigonal pertuis. Collection between the mesh and bladder eliminated by a sustrigonal channel. 06Jan06 urethrocystoscopy.

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Patient	Event	Onset-Resolved Dates	Outcome	Relationship	(Serious Category) Comments
5005	Exposure of the prosthesis on the necrosis of the vaginal dome scar	13Dec04-14Apr05	Recovered	Probable	(Surgical/medical intervention) Augmentin 1g x2/dy. Colposeptine 1/dy for 3 wk then colpotrophine. 04Mar05- partial ablation of the prosthesis and vaginal debridement.
7003	Haematoma abscess	30Apr04-07May04	Recovered	Probable	(Hospitalisation) Augmentin and catheterisation.
7003	Exposure of mesh. Resection of mesh.	14Jun04-08Jul04	Recovered	Probable	(Hospitalisation) Mesh exposure resection
7004	Post operative urinary incontinence	06May04-08Jul04	Recovered	Probable	(Hospitalisation, medical/surgical intervention) Transobturator sling placed by suburethral approach Incontinence caused by prolapse correction.
7013	Urinary incontinence revealed by the prolapse repair	01Jul03-23Feb05	Recovered	Probable	(Surgical/medical intervention) Treatment-TVTO. De novo incontinence caused by prolapse repair.
7016	Urinary incontinence revealed by the prolapse repair	13Dec04-03Mar05	Recovered	Probable	(Surgical/medical intervention) Treatment-TVTO. Urinary incontinence caused by prolapse repair.

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Patient	Event	Onset-Resolved Dates	Outcome	Relationship	(Serious Category) Comments
7017	Urinary incontinence revealed by the prolapse repair	12Dec04-01Mar05	Recovered	Probable	(Surgical/medical intervention) Treatment-TVTO. Urinary incontinence caused by prolapse repair.
7020	Stress urinary leakage	24Nov04-15Apr05	Recovered	Probable	(Surgical/medical intervention) Excellent result following TVT-O surgery on 15Apr05.
8001	Posterior failure with elytrocele & sigmoidocele	25Nov04-09Sep05	Recovered	Probable	(Hospitalisation, surgical/medical intervention) 26Jul05 elytrocele repair by vaginal route with sigmoid ligature and right spinofixation with 2 vaginal flap. Excellent results. No more prolapse-vaginal mucous soft & healthy.
8003	Exposure of the mesh prolene soft	20Oct04-09Sep05	Recovered	Probable	(Hospitalisation, surgical/medical intervention) Colpoptrophine + opalgyne. 18Jan05 surgery. 25Jul05 hospitalisation. Iterative exeresis of mesh for minor exposure. Few sutures at the level of the vaginal fundus.

Source: Appendices 16.2.7.1, 16.2.7.3 and 16.2.7.4

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12.3.4 ANALYSIS AND DISCUSSION OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

No analysis was planned or undertaken.

12.4 CLINICAL LABORATORY EVALUATION

Not performed in this study.

12.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Additional operations are summarised in Table 14.3.1.1 and listed in Appendix 16.2.7.1.

Nine (10.0%) patients had insertion of TVT or TVT-O, five (5.6%) patients had excision of mesh and two (2.2%) patients had repair of recurrence. Section of adhesions, section of TVT-O and vesico vaginal fistula were each reported in one patient. Three (3.3%) patients had an additional operation classified as 'other'; patient 4001 had examination with local anaesthesia which showed 'suspicion of no vaginal cicatrisation', patient 5001 had cholecystectomy for 'hepatic colic' and patient 5003 had uretrocystoscopy rectoscopy for 'haematuria, dysuria, UTI'.

12.6 SAFETY CONCLUSIONS

The intra-operative complication rate in this study was low (5.6%). The major post-operative complication reported at 6 weeks was urinary infection (15 [16.9%] patients). Haematoma and abscess were reported by 4 (4.5%) and one (1.1%) patient respectively. One case of vesico vaginal fistula, which resolved with surgery, was reported. The adverse events reported most commonly during the 12-month follow-up period were UTI (20 [22.2%] patients) and urinary incontinence (24 [26.7%] patients). Twenty-seven SAEs were reported and 18 of these were considered probably related to the study device or procedure.

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13. DISCUSSION AND OVERALL CONCLUSIONS

The results of the study do not fulfil the criteria of success, which was pre-defined as a prolapse recurrence rate of less than 20%. Sixteen patients were reported as failures by reason of having a prolapse of ICS Stage II or above, or requiring surgical re-intervention. However in 10 of the anatomical failures the leading edge was inside the introitus. Only one patient had a prolapse of ICS Stage III with the leading edge beyond the hymen. Therefore the study demonstrates reasonable success rates and the recurrence rate observed compares favourably with re-operation rates of around 30% using traditional vaginal approaches in other studies [5-7].

One factor which may have influenced the recurrence rate in this study was the limited experience of the investigators with the POP-Q assessment and stage classification system. This system was not routinely used in their clinical practice, and only minimal training was provided prior to the start of the study. This clearly led to some over-grading of prolapse, as demonstrated by the unintended presence of Stage II prolapse patients in the study, and was likely to have contributed to the wide variation in recurrence rates observed between centres (0-50%).

Review of graphic images of POP-Q for each recurrence demonstrated atypical recurrence. The shape of the TVM mesh was never designed to support the bladder neck and the urethra. In case of caudal retraction of the anterior mesh, an atypical cystocèle may occur with a limited bladder herniation anterior to the inter-ureteric ridge. Absence of a suburethral sling may further aggravate the likelihood of this occurring. Despite efficient support of the deep anterior vaginal wall and the vaginal cuff and according to the POP Q quantification, these patients are regarded as failure with a stage II prolapse at the postoperative evaluation.

The number of patients reporting sexual activity limited by prolapse at 12 months was reduced to 6.9% from the baseline figure of 32.2%. The incidence of dyspareunia at 12 months was 3 (3.4%) compared with 5 (5.6%) at baseline. The incidence of dyspareunia at baseline in 61 patients who were sexually active was 4 (7%). At 12 months, 3 patients of the 40 who were sexually active (8%) reported dyspareunia. All 3 were new onset dyspareunia.

Moderate or severe vaginal retraction was reported in 11 patients. Nine patients experienced mesh exposure during the 12 month follow up, 5 of whom underwent surgical re-intervention to correct.

Substantial improvements in QOL, particularly with respect to the PSI, were observed (reduced from 13.9 at baseline to 3.1 at 12 months). Activities of daily living QOL scores also improved over the 12-month study period (3.4 reduced to 0.4). Thus, in this study, improvements in QOL were observed, even when

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the procedure was not a perfect anatomical success, and this has been seen in another study [17]. This finding is consistent with published data indicating that there is a reduction in QOL once the leading edge is outwith the hymen [16] and has been incorporated into a proposed randomised controlled trial in which anatomical and QOL measures are weighted equally as outcome measures.

This study demonstrates low mesh exposure and complication rates and an acceptable safety profile. Further follow-up of these patients to 5 years post-procedure is planned.

A similar study using TVM was conducted concurrently in 85 patients at 3 sites in the US [17]. The 12-month recurrence rate in this study was 12.0% with an upper 90% CI of 19.6, thus meeting the pre-defined success criteria. As in the French study, substantial improvements in QOL were observed.

There were a number of differences between the two studies which may account for the differing success rates:

- Either previous or concurrent hysterectomy was required in the French study (20.0% previous hysterectomy, 80% concurrent) but this was not a fixed requirement in the US study (67.1% previous, 20.0% concurrent and 12.9% with uterine preservation).
- Total TVM was placed in all but one of the patients in the French study (98.9%) whilst in the US study, investigators had the options of placing anterior (30.6%), posterior (9.4%) or total TVM (60.0%).
- In the French study, only 51 (56.7%) had a transgluteal approach compared to the US study where all of the total TVM repairs were performed using the transgluteal approach. The remaining 39 (43.3%) patients in the French study had mesh placed by the vaginal route only, with direct fixation of the implant on the sacrospinous ligament.
- There were 8 French sites compared with 3 US sites, and this may have led to the increased variability in the results observed between French sites.
- The POP-Q scoring system is not routinely used in France whereas it is more commonly used in the US.

In conclusion, the TVM procedure used in this study has been further adapted with design of the needle and cannula to protect the attachment points for the mesh that turned out to be at risk using the TVM tools. The early results of studies using the end product appear to confirm the advantage offered by this evolution [19, 20].

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14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

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